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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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David Mu

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07/27/2006

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EXAMINER

GIBBS, TERRA C

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/073,060	Applicant(s) MU ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,9-12,14,22-24,33-35 and 39-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,9-12,14,22-24,33-35 and 39-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 February 1002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 15, 2006 has been entered.

Claims 34 and 52 have been amended.

Claims 1-3, 9-12, 14, 22-24, 33-35, 39-64 are pending in the instant application.

Claims 1-3, 9-12, 14, 22-24, 33-35, 39-64 have been examined on the merits.

Response to Amendment

Applicants Amendment filed May 15, 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 15, 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 59-64 are indefinite because they recite the terms, "first indirect measure" or "second indirect measure". The terms, "first indirect measure" or "second indirect measure" are not defined by the claim(s), the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of such terms.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-12, 14, 22-24, 33-35, 39-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

At the outset it is noted that the rejected claims do not recite any sequence identifier relating to hepsin. The specification discloses GenBank Accession Number M18930, which corresponds to the human Hepsin gene represented by SEQ ID NO:1 in the instant invention (see page 36). The rejected claims encompass methods for diagnosing a cancer and methods for monitoring the efficacy of a therapeutic treatment regimen through determining the levels of hepsin gene copy number, mRNA, or protein. The specification at page 21, lines 12-19 defines "hepsin" as referring to hepsin nucleic acid (DNA and RNA), protein, their polymorphic variants, alleles, mutants, and interspecies homologs that have substantial nucleotide sequence homology with the nucleotide sequence of SEQ ID NO:1 and GenBank Accession Number M18930, human hepsin mRNA. The prior art teaches hepsin genes with many different GenBank Accession Numbers. For example, the art teaches GenBank Accession Number BC025716, NM_008281, NM_182983, NM_017112, NM_002151, X70900, X07732, and AF030065, X07002. The claims are directed to encompass a broad range of hepsin sequences of highly variant structures (e.g. nucleic acid sequence), which have not been described in the specification and whose structure could not be envisioned by the skilled artisan based on the disclosure of the specification.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive

means as words, structures, Figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, Figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing

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identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of hepsin, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO:1, but not all the sequences encompassed by the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Thus, because one of skill in the art could not envision any methods for diagnosing a cancer or methods for monitoring the efficacy of a therapeutic treatment regimen through determining the levels of hepsin gene copy number, mRNA, or protein, other than those described in the instant specification, one of skill would not be convinced that applicants were in possession of any hepsin sequences that are heretofore undescribed. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Claims 1-3, 9-11, 39, 40, 44, 45, and 49-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing an ovarian cancer in a mammal *ex vivo*, or a method for monitoring the efficacy of an ovarian therapeutic treatment regimen in a patient *ex vivo*, comprising measuring hepsin gene copy number, does not reasonably provide enablement for a method for diagnosing *any* cancer in a mammal *in vivo* or a method for monitoring the efficacy of *any* cancer *in vivo*, comprising measuring hepsin gene copy number. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

Claims 1-3, 9-11, 39, 40, 44, 45, and 49-64 are drawn to methods for diagnosing cancer in a mammal or methods for monitoring the efficacy of a treatment regimen in a patient, comprising measuring hepsin gene copy number, wherein the language of said claims encompasses both *in vivo* and *ex vivo* applicability.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter.

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1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). The claims are so broad to include methods of diagnosing cancer in a mammal, including but not limited to ovarian lung, breast, and prostate cancer, comprising measuring hepsin gene copy number. The claims are also so broad to include methods for monitoring the efficacy of a treatment regimen in a patient, including but not limiting to an ovarian, lung, breast, and prostate treatment regimen, comprising measuring hepsin gene copy number. First, it is noted that the instant specification teaches that the hepsin gene is not amplified in prostate tumor. For example, the instant specification at page 65, line 6 discloses, “Hepsin gene was not amplified in the tested prostate tumor samples”. Second, in Table 4, it is taught that out of 33 lung tumor samples tested, only one overexpressed the hepsin gene copy number. Table 4 also teaches that out of 35 breast tumor samples tested, only one overexpressed the hepsin gene copy number. It is unclear how 1/33 or 1/35 lung and breast samples showing overexpression of hepsin

is seen as being statistically significant. It is highly unpredictable to extrapolate findings from this aforementioned data to the methods as broadly claimed.

Scope of the invention. The scope of the invention is very broad, claiming methods of diagnosing cancer in a mammal and methods for monitoring the efficacy of a treatment regimen in a patient *in vivo*, comprising measuring hepsin gene copy number. The specification does not specify any examples of such well-established *in-vivo* model systems or evidence for the predictable association of hepsin expression to correlate with all cancers or treatment regimens. As alluded to in the Nature of the invention, even if applicants would enable methods of diagnosing cancer in a mammal and methods for monitoring the efficacy of a treatment regimen in a patient *ex vivo*, (e.g. lung or breast cancer) through correlation to an over-expressed hepsin gene copy number, the data still appears to lack any statistical significance.

State of the art. The prior art does not disclose methods of diagnosing cancer in a mammal or methods for monitoring the efficacy of a treatment regimen in a patient *ex vivo* or *in vivo*, comprising measuring hepsin gene copy number, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the ability of a such methods of diagnosis and monitoring treatment efficacy *in vivo*, to have such far-reaching effects such as into the manifestation of any cancer, results in the invention being unpredictable in terms of its use as presently claimed. Furthermore, the prior art teaches much unpredictability regarding the role of hepsin in tumor growth. For example, Tanimoto et al. (Applicants reference A63 in the information disclosure statement filed June 17, 2002) states that the role of hepsin in

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tumor cell growth and spread is unclear (see page 2887, first column). The post-date filing art provides an example of this state of the art in their teaching that "Gene association studies typically are wrong" (Lucentini, The Scientist, Vol. 18 Issue 24, 20, Dec. 20, 2004). Lucentini teach that "Reproducible gene-disease associations are few and far between" (see page 1). The reference continues to teach that "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated" (see page 2, 4th paragraph). As such, the state of the art provides further unpredictability regarding the reliable practice of gene-association studies and specifically the hepsin gene.

Number of working examples and Guidance provided by Applicant. The examples that are taught in the specification include Example I and Table 4, wherein amplification (overexpression) of the hepsin gene copy number was seen in 3 out of 8 ovarian tumor cell lines *in vitro* and 5 out of 29 ovarian tumor samples *ex vivo*. The Example and Table also teaches that 1 out of 33 lung and 35 breast tumor samples exhibit hepsin gene copy overexpression *ex vivo*, and hepsin gene was not amplified in the tested prostate tumor samples. Considering the unpredictability surrounding the extrapolation of data from experiments using different tumor samples and different, undisclosed measures of significance, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention

commensurate in scope with these claims.

Level of skill in the art. The level of skill involved in relating the unknown amount of hepsin gene copy number to every type of cancer is very high if not impossible. Additionally, the functional use of such an undisclosed property of hepsin detection is seen, in this instance, to be prophetic.

In the instant case, as discussed above, in a highly unpredictable art where the ability of gene association studies to be credible and wherein the functions of hepsin are still not certain, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized variant uses for the methods of diagnosing cancer in a mammal and methods for monitoring the efficacy of a treatment regimen in a patient, comprising measuring hepsin gene copy number as broadly claimed (i.e. encompassing *in vivo* methods and any type of cancer). Thus, given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example *in vivo* and the teachings in the prior art balanced against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to perform the methods commensurate in scope with these claims.

Claims 12, 14, 41, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

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which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a full enablement rejection.

Claims 12, 14, 41, and 46 are drawn to a method for diagnosing a breast or a lung cancer in a mammal, comprising measuring hepsin mRNA expression, wherein the language of said claims encompasses both *in vivo* and *ex vivo* applicability.

The test of enablement and factors for determining enablement are as described above in the scope of enablement rejection against claims 1-3, 9-11, 39, 40, 44, 45, 49, 50, and 52-64.

Nature of the invention. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). First, it is noted that the instant specification teaches that the hepsin mRNA is amplified (overexpressed) in ovarian and prostate tumor samples *ex vivo* (see page 43, lines 27-29 and Tables 2 and 3). The prior art teaches that hepsin mRNA is amplified (overexpressed) in ovarian and prostate tumor samples. For example, see Tanimoto et al. (Applicant's reference A63 in the information disclosure statement filed June 17, 2002), Tanimoto et al., *Journal of the Society for Gynecological Investigation*, 1997 Vol. 14, page 577, (Applicant's reference C06 in the information disclosure statement filed November 4, 2002), Tanimoto et al. *Proceedings of the American Association for Cancer Research*, 1997 Vol. 38, Abstract #2765 (Applicant's reference C05 in the information disclosure statement filed November 4, 2002), and WO 98/41656 (Applicant's reference B05 in the

information disclosure statement filed August 16, 2002). The specification also teaches that out of 33 lung tumor samples tested, and out of 35 breast tumor samples tested, only one overexpressed the hepsin gene copy number in each tumor sample set. The specification and the prior art are both silent regarding hepsin mRNA overexpression in lung or breast tumor samples. It is highly unpredictable to extrapolate findings from this aforementioned data to the claimed methods since the instant specification discloses that overexpression of gene copy is not correlated to overexpression of mRNA levels. For example, the instant specification at page 3, third paragraph discloses, "The overexpression of certain well known genes, for example, *c-myc*, have been observed at fairly high levels in the absence of gene amplification". For further explanation, see Yoshimoto et al., 1986 Japanese Journal of Cancer Research, Vol. 77, pages 540-545 (Applicant's reference A71 in the information disclosure statement filed November 4, 2002).

Scope of the invention. The scope of the invention is very broad, claiming a method for diagnosing a breast or a lung cancer in a mammal, comprising measuring hepsin mRNA expression, wherein the language of said claims encompasses both *in vivo* and *ex vivo* applicability. As alluded to in the Nature of the invention, even if applicants would enable a method for diagnosing an ovarian or prostate cancer in a mammal *ex vivo*, comprising measuring hepsin mRNA expression, a correlation to breast or lung cancer is lacking.

State of the art. The prior art does not disclose methods for diagnosing a breast or lung cancer in a mammal *ex vivo* or *in vivo*, comprising measuring hepsin mRNA

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expression, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the ability of a such a method for diagnosing a breast or lung cancer in a mammal *ex vivo* or *in vivo*, to have such far-reaching effects such as into the manifestation of breast or lung cancer, results in the invention being unpredictable in terms of its use as presently claimed. Furthermore, the prior art teaches much unpredictability regarding the role of hepsin in tumor growth. For example, Tanimoto et al. (Applicants reference A63 in the information disclosure statement filed June 17, 2002) states that the role of hepsin in tumor cell growth and spread is unclear (see page 2887, first column). The post-date filing art provides an example of this state of the art in their teaching that "Gene association studies typically are wrong" (Lucentini, The Scientist, Vol. 18 Issue 24, 20, Dec. 20, 2004). Lucentini teach that "Reproducible gene-disease associations are few and far between" (see page 1). The reference continues to teach that "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated" (see page 2, 4th paragraph). As such, the state of the art provides further unpredictability regarding the reliable practice of gene-association studies and specifically the hepsin gene.

Number of working examples and Guidance provided by Applicant. The examples that are taught in the specification include Examples II and III and Tables 2 and 3, wherein amplification (overexpression) of hepsin mRNA was seen at high levels in ovarian and prostate tumor tissue *ex vivo*. Considering the unpredictability

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surrounding the extrapolation of data from experiments using different tumor samples and different, undisclosed measures of significance, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention as claimed as it relates to breast and lung cancer.

Level of skill in the art. The level of skill involved in relating the unknown amount of hepsin mRNA expression to ovarian and prostate to breast and lung cancer is very high if not impossible. Additionally, the functional use of such an undisclosed property of hepsin detection is seen, in this instance, to be prophetic.

In the instant case, as discussed above, in a highly unpredictable art where the ability of gene association studies to be credible and wherein the functions of hepsin are still not certain, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized variant uses for the diagnosing a breast or a lung cancer in a mammal, comprising measuring hepsin mRNA expression as broadly claimed (i.e encompassing *in vivo* methods). Thus, given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example *in vivo* and the teachings in the prior art balanced against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to practice the methods as claimed.

Claims 22-24, 33-35, 42, 43, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for monitoring the efficacy of an ovarian or prostate therapeutic treatment regimen in a patient *ex vivo*, comprising measuring hepsin mRNA, or a method for monitoring the efficacy of an ovarian, prostate, or lung therapeutic treatment regimen in a patient *ex vivo*, comprising measuring hepsin protein, does not reasonably provide enablement for a method for monitoring the efficacy of *any* cancer *in vivo*, comprising measuring hepsin mRNA or hepsin protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

Claims 22-24, 33-35, 42, 43, 47, and 48 are drawn to a method for monitoring the efficacy of a treatment regimen in a patient, comprising measuring hepsin mRNA or hepsin protein, wherein the language of said claims encompasses both *in vivo* and *ex vivo* applicability.

The test of enablement and factors for determining enablement are as described above in the scope of enablement rejection against claims 1-3, 9-11, 39, 40, 44, 45, 49, 50, and 52-64.

Nature of the invention. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001). The claims are

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so broad to include a method for monitoring the efficacy of a treatment regimen in a patient, including but not limiting to an ovarian, lung, breast, and prostate treatment regimen, comprising measuring hepsin mRNA or hepsin protein. First, it is noted that the instant specification teaches that the hepsin mRNA is amplified (overexpressed) in ovarian and prostate tumor samples *ex vivo* (see page 43, lines 27-29 and Tables 2 and 3). The prior art teaches that hepsin mRNA is amplified (overexpressed) in ovarian and prostate tumor samples. For example, see Tanimoto et al. (Applicant's reference A63 in the information disclosure statement filed June 17, 2002), Tanimoto et al., Journal of the Society for Gynecological Investigation, 1997 Vol. 14, page 577, (Applicant's reference C06 in the information disclosure statement filed November 4, 2002), Tanimoto et al. Proceedings of the American Association for Cancer Research, 1997 Vol. 38, Abstract #2765 (Applicant's reference C05 in the information disclosure statement filed November 4, 2002), and WO 98/41656 (Applicant's reference B05 in the information disclosure statement filed August 16, 2002). The prior art also teaches that hepsin protein is amplified (overexpressed) in ovarian, lung, and prostate tumor samples. For example, see Zacharski et al., Thromb Haemost, 1998 Vol. 79, pages 876 and 877 (Applicant's reference A72 in the information disclosure statement filed November 4, 2002) and Magee et al., Cancer Research, 2001 Vol. 61, pages 5692-5696 (Applicant's reference A44 in the information disclosure statement filed November 4, 2002). The specification also teaches that out of 35 breast tumor samples tested and 33 lung tumor samples tested, only one overexpressed the hepsin gene copy number in each tumor sample set. The specification and the prior art are both silent regarding hepsin mRNA

or protein overexpression in breast tumor samples. It is highly unpredictable to extrapolate findings from this aforementioned data to the claimed methods since the instant specification discloses that overexpression of gene copy is not correlated to overexpression of mRNA levels. For example, the instant specification at page 3, third paragraph discloses, "The overexpression of certain well known genes, for example, *c-myc*, have been observed at fairly high levels in the absence of gene amplification". For further explanation, see Yoshimoto et al., 1986 Japanese Journal of Cancer Research, Vol. 77, pages 540-545 (Applicant's reference A71 in the information disclosure statement filed November 4, 2002).

Scope of the invention. The scope of the invention is very broad, claiming methods for monitoring the efficacy of a treatment regimen in a patient *in vivo*, comprising measuring hepsin mRNA or hepsin protein. The specification does not specify any examples of such well-established *in-vivo* model systems or evidence for the predictable association of hepsin expression to correlate with all cancer treatment regimens. As alluded to in the Nature of the invention, even if applicants would enable methods for monitoring the efficacy of a treatment regimen in a patient *ex vivo*, (e.g. ovarian, lung, and prostate) through correlation to an over-expressed hepsin mRNA or hepsin protein, a correlation to breast cancer is lacking.

State of the art. The prior art does not disclose methods for monitoring the efficacy of a treatment regimen in a patient *ex vivo* or *in vivo*, comprising measuring hepsin mRNA or hepsin protein, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the ability of a such

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methods of diagnosis and monitoring treatment efficacy *in vivo*, to have such far-reaching effects such as into the manifestation of any cancer, results in the invention being unpredictable in terms of its use as presently claimed. Furthermore, the prior art teaches much unpredictability regarding the role of hepsin in tumor growth. For example, Tanimoto et al. (Applicants reference A63 in the information disclosure statement filed June 17, 2002) states that the role of hepsin in tumor cell growth and spread is unclear (see page 2887, first column). The post-date filing art provides an example of this state of the art in their teaching that "Gene association studies typically are wrong" (Lucentini, The Scientist, Vol. 18 Issue 24, 20, Dec. 20, 2004). Lucentini teach that "Reproducible gene-disease associations are few and far between" (see page 1). The reference continues to teach that "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated" (see page 2, 4th paragraph). As such, the state of the art provides further unpredictability regarding the reliable practice of gene-association studies and specifically the hepsin gene.

Number of working examples and Guidance provided by Applicant. The examples that are taught in the specification include Examples II and III and Tables 2 and 3, wherein amplification (overexpression) of hepsin mRNA was seen at high levels in ovarian and prostate tumor tissue *ex vivo*. Example 1 and Table 4 teaches that 1 out of 35 breast tumor samples and 1 out of 33 lung tumor samples exhibit hepsin gene copy overexpression *ex vivo*. Considering the unpredictability surrounding the

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extrapolation of data from experiments using different tumor samples and different, undisclosed measures of significance, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention commensurate in scope with these claims.

Level of skill in the art. The level of skill involved in relating the unknown amount of hepsin mRNA or hepsin protein to every type of cancer is very high if not impossible. Additionally, the functional use of such an undisclosed property of hepsin detection is seen, in this instance, to be prophetic.

In the instant case, as discussed above, in a highly unpredictable art where the ability of gene association studies to be credible and wherein the functions of hepsin are still not certain, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized variant uses for the methods for monitoring the efficacy of a treatment regimen in a patient, comprising measuring hepsin mRNA or hepsin protein as broadly claimed (i.e. encompassing *in vivo* methods and any type of cancer). Thus, given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example *in vivo* and the teachings in the prior art balanced against the high skill level in the art, it is the position of the Examiner that it would require undue experimentation for one of skill in the art to perform the methods commensurate in scope with these claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
July 23, 2006

A handwritten signature in black ink, appearing to read "Terra C. Gibbs", is written over the typed name.